chemotherapy or HIV. Therefore, flight attendants and others say that airplane cabin air should be held to higher standards than workplaces.

Pressure from passengers may be a major contributing factor in encouraging airlines to increase fresh air. In the August issue of *Consumer Reports*, airlines were ranked according to levels of carbon dioxide in airplane cabins and criticized for the low amounts of fresh air. *Consumer Reports* recommended that passengers choose airlines according to the amounts of fresh air they circulate. They also recommended that the FAA set a comfort standard of 1,000 ppm.

Double-Edged Sword?

Although individuals with genetic disorders and diseases such as cancer, AIDS, diabetes, or Alzheimer's may view the potential of gene therapy as just the weapon they're looking for, other people perceive the "slicing and dicing" of genetic material as a potential double-edged sword. Scientists are attempting to estimate the real risks associated with gene therapy.

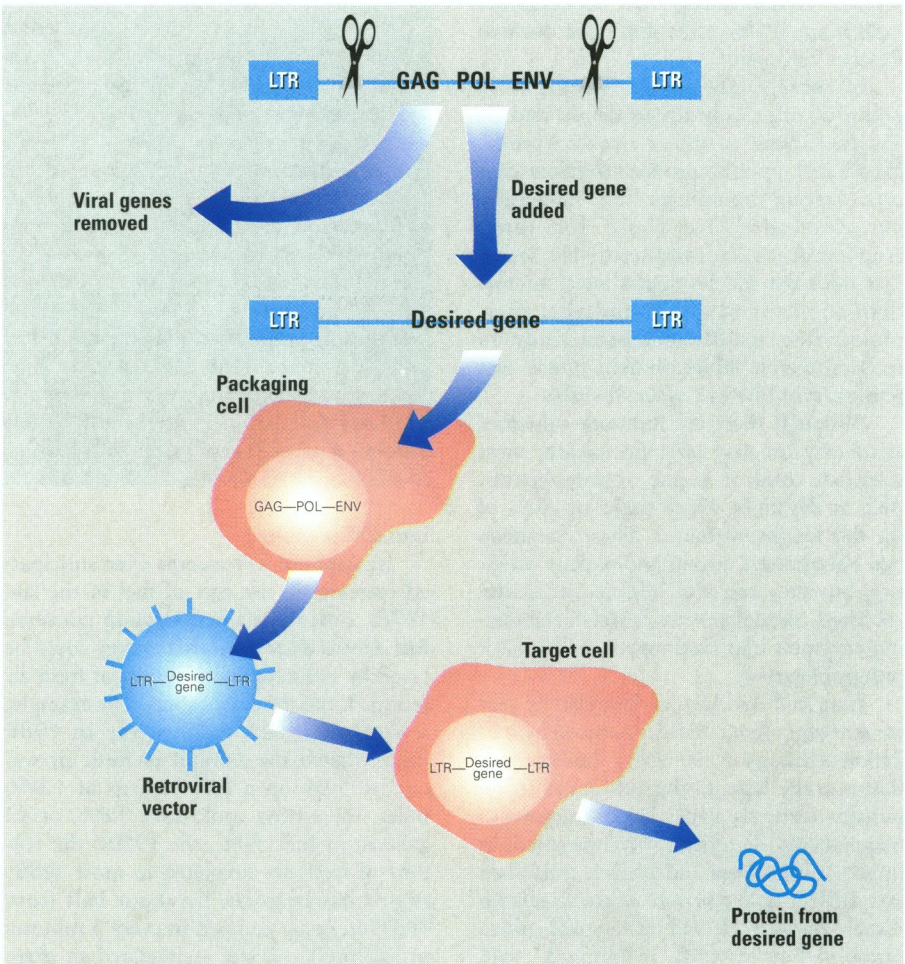
Most current gene therapies use retroviral vectors to transfer a therapeutic gene into the cells of a patient who lacks a normally functioning copy of the gene. Retroviral vectors are made by deleting portions of a retroviral genome and replacing the deleted viral genes with the therapeutic gene. The resulting vector integrates a DNA copy of its genome, containing the therapeutic gene, into the genome of a host cell, but because of the missing viral genes the vector cannot be replicated like a normal retrovirus.

Typically, bone marrow cells are removed and exposed to the vector in culture. The cells containing the therapeutic gene are then infused back into the patient. The fear is that the vector may integrate its DNA copy near a gene involved in regulation of growth or development of the cell and interfere with the normal regulatory processes, causing the cell to become cancerous. Although, says toxicologist Richard Irwin of NIEHS, "there is absolutely a finite probability that it will occur," the risk of insertional mutagenesis is believed to be very low. The difficulty comes in trying to determine exactly what "very low" means in terms of absolute risk to humans from gene therapy.

Scientists are concerned about other potential side effects of the process of gene therapy. First, it is not currently possible to target a vector carrying a therapeutic gene to a specific cell population. Expression of the gene in nontargeted cells may interfere with regulation of cell processes or metabolic pathways. Second, the transduced cells may contain a selective growth advantage, enabling their progeny to predominate in the host. When such cells are introduced into a patient during gene therapy, they represent a population carrying a "first hit" insertional event that may put the patient at increased risk for additional mutational events leading potentially to tumor formation. Third, retroviral vector preparations may be contaminated by virions containing packaging cell RNA. In theory, this RNA could be reverse-transcribed, integrate in the genome of the recipient cells, and express a product that could disrupt normal cell functioning.

The risk posed by insertional mutagenesis is a particular concern for extending gene therapy to the treatment of conditions such as diabetes or hemophilia where substantial numbers of people would be candidates for the therapy and might be treated early in their lives. A population of cells carrying a first hit insertional event would put such people at an increased risk throughout the remainder of their lives.

As gene therapies are expanded for the treatment of more diseases, the sheer numbers of people involved makes it more likely that even a relatively infrequent event may result in an unacceptably high risk. Irwin and his colleagues at the NIEHS are developing studies to attempt to evaluate the extent of this risk. In these studies, researchers will expose mice and rats to retroviral vectors in a number of ways. These vectors contain marker genes which allow the researchers to determine the most effective method of integration of the vector into the new cell genome. The animals are allowed to live out their life spans, and researchers then examine them to see if they developed tumors, and if so, if the tumors contained DNA from the retroviral vector. The information from these studies will be used to estimate gene therapy's risk and may help regulators evaluate the safety of cutting edge technology.



Cut and paste. Retroviral vectors are made by transferring a modified retrovirus into a packaging cell which produces the desired protein in a target cell.